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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,101	12/30/2005	Akira Kato	0425-1236PUS1	6760

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EXAMINER	
SOROUSH, ALI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
09/03/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,101	KATO ET AL.	
	Examiner	Art Unit	
	ALI SOROUSH	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13-15,17-22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13-15,17-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's response filed on 04/27/2010 to the Office Action mailed on 12/29/2009 is acknowledged.

Status of the Claims

Claims 1, 3-11, 13-15, 17-22 and 24 are currently pending examination for patentability.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. The rejection of claims 1, 3-11, 13-15, 17, and 24 under 35 U.S.C. 103(a) as being unpatentable over Chaubal et al. (US Patent Application 2004/0245662,

Published 12/09/2004, Filed 11/07/2003) in view of Thumm et al. (US Patent 6221332 B1, Published 04/24/2001) **is maintained**.

Applicant Claims

A method of producing ultrafine drug particles comprising the steps of: dissolving a drug in a good solvent, mixing the drug suspension in a poor solvent, and subjecting the mixture to high-pressure homogenization. Wherein the mixing occurs such that the poor solvent is circulated into the homogenizer and then the drug-containing solution is added to the circulating solution.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Chaubal et al. teach, a "[m]ethod for preparing submicron particles of antineoplastic agents." (See title). "The particles generally produced have an average particle size of less than about 1000 nm and are not rapidly soluble." (See abstract). "Preferably the organic compound or the pharmaceutically active compound is poorly water-soluble. What is meant by 'poorly water soluble' is a solubility of the compound in water of less than about 10 mg/ml, and preferably less than 1 mg/ml." (See paragraph 0046). "The process for preparing the particles can be separated into four general categories. Each of the categories of processes share the steps of: (1) dissolving an organic compound in a water miscible first solvent to create a first solution, (2) mixing the first solution with a second solvent of water to precipitate the organic compound to create a pre-suspension, and (3) adding energy to the pre-suspension in the form of high-shear mixing or heat, or a combination of both, to provide a stable form of the

organic compound having the desired size ranges defined above. The mixing steps and adding energy step can be carried out in consecutive steps or simultaneously." (See paragraph 0053). "The energy-addition step involves adding energy through sonication, homogenization, countercurrent flow homogenization, microfluidization, or other methods of providing impact, shear or cavitation forces … In one preferred form of the invention, the energy addition step is effected by a piston gap homogenizer such as one sold by Avestin Inc. under the product designation EmulsiFlex-C160." (See paragraph 0077). In a preferred embodiment, "2.08 g of carbamazepine was dissolved into 10 mL of NMP [N-methyl-2-pyrrolidinone] . 1.0 mL of this concentrate was subsequently dripped at 0.1 ml/min into 20 ml of a stirred solution of 1.2% lecithin and 2.25% glycerin … The predispersion was next homogenized cold … for 35 minutes at 15,000 psi. The pressure was increased to 23,000 psi and homogenization was continued for another 20 minutes." (See paragraph 0142). "The method … further compris[es] removing the liquid phase of the suspension to form a dry powder of the particles." (See claim 27). "[W]herein the removing of the liquid phase is selected from the group consisting of: evaporation, rotary evaporation, lyophilization, freeze-drying, dia-filtration, centrifugation, force-field fractionation, high-pressure filtration, and reverse osmosis." (See claim 28). For the foregoing reasons the instant method is anticipated.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Chaubal et al. does not teach the mixing step such that the poor solvent is circulated into the homogenizer and then the drug-containing solution is added to the circulating solution.

Chaubal et al. further does not teach a homogenizer with an online injector, a reservoir, booster pump, and emulsifier. These deficiencies are cured by the teachings of Thumm et al.

Thumm et al. teach a Microfluidizer with multiple streams. (See title). The apparatus comprises two hydraulic pumps, which the Examiner has interpreted to read on the instantly claimed booster pump. The apparatus further comprises two reservoirs which are attached to source material pistons for injecting the material into the apparatus pipes, which the Examiner has interpreted to read on the instantly claimed reservoir and online injector. The two liquids to be mixed come together in the mixer/reactor to form the nanoparticles, which the Examiner has interpreted to read on the instantly claimed emulsifier. (See column 7, Lines 14-67, column 8, Lines 1-26 and Figure 4). Thum et al. teach, "It has now been recognized that for precipitation reaction, the reaction kinetics are such that significant precipitation nucleation and reaction will have occurred during premixing, well prior to introduction of the mixture into the high energy mixing zone. As a result, the nuclei formed in the premixture are less uniform than when the mixing/reacting is performed with the apparatus of the present invention ... The present invention produces nanosize product particles of a smaller, more uniform size distribution that enhances use of the products for various applications ..." (See column 2, Lines 5-30).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art to combine the teachings of Chaubal et al. with Thumm et al. One would have been motivated to do so because Thumm et al. teach that using the modified Microfluidizer taught by Thumm et al. would result in a more uniform particle size distribution of the nanoparticles formed by the teaching of Chaubal et al. For the foregoing reasons, the instant method would have been obvious to one of ordinary skill in the art at the time of the instant invention.

Response to Applicant's Arguments

Applicant argues that the instant method provides better results over the prior art methods. Applicant indicates that the comparative examples presented show an unexpected result in producing average particle sizes that are very small with applicant's instant method relative to those found in the prior art. Applicant's argument has been fully considered but found not to be persuasive. It is the Examiners position that data of unexpected results is not commensurate in scope with the instant claims. The claims are broader than what is tested in the comparative examples. The claims are directed to a broad range of solvent concentrations and solvent types, however the data presented is directed to a specific solvent type and amount of solvent being used. Further, Applicant has not provided a true side by side comparison with the closest prior art, Chaubal et al. For the foregoing reasons, the rejection of claims 1, 3-11, 13-15, 17, and 24 under 35 U.S.C. 103(a) is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ali Soroush whose telephone number is (571) 272-9925. The examiner can normally be reached on Monday through Thursday 8:30am to 5:00pm E.S.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number For the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ali Soroush
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